ATTORNEY DOCKET NO.:599 1338

#24

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No.:	~~4,948,045~~	)
Granted:	August 14, 1990	)
Patentees:	Antonio ZIGGIOTTI and Michele DISCHIENA)	)
Assignee:	Altergon, S.A.	)
FOR:	SALT OF DICLOFENAC WITH A PYRROLIDINE COMPOUND AND PHARMACEUTICAL COMPOSITIONS WHICH CONTAIN IT	

Attention: BOX PATENT EXTENSION
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR EXTENSION OF PATENT TERM
PURSUANT TO 35 U.S.C. §156

Sir:

Applicant, Altergon S.A., a corporation created and existing under the Laws of Switzerland, represents that it is the assignee of the entire interest in and to Letters Patent United States No. 4,948,045 granted to Ziggiotti et al., on August 14, 1990 for Salt of Diclofenac With a Cyclic Pyrollidine Compound and Pharmaceutical Compositions Which Contain It, by virtue of an Assignment from the inventors thereof to Altergon S.A. and Ricefarma S.R.L., recorded November 9, 1987 at Reel 004795, Frame 0836 and an Assignment from Altergon S.A. and Ricefarma S.R.L. to Altergon S.A. at Reel 004825, Frame 0014 on February 10, 1988. Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. §156(a), Altergon S.A., hereby requests an extension of the patent term of U.S. Patent

No. 4,948,045. A Revocation of Original Power of Attorney and Grant of New Power of Attorney is being filed herewith, authorizing the registered practitioners of Abelman, Frayne & Schwab to act on behalf of Applicant, with correspondence and communications to be directed as set forth therein and in section (15) of this Application.

The following information is submitted in accordance with 35 U.S.C. §156(d) and 37 C.F.R. §1.710 *et seq.*, and follows the numerical sequence and format as set forth in 37 C.F.R. §1.740(a):

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

The approved product is FLECTOR® PATCH (diclofenac epolamine topical patch) 1.3%, identified as follows:

Chemical Name:

2[(2,6-dichlorophenyl)-amino]benzeneacetic acid), 2-(pyrrolidin-1-yl)ethanol salt

Generic Name:

Diclofenac epolamine

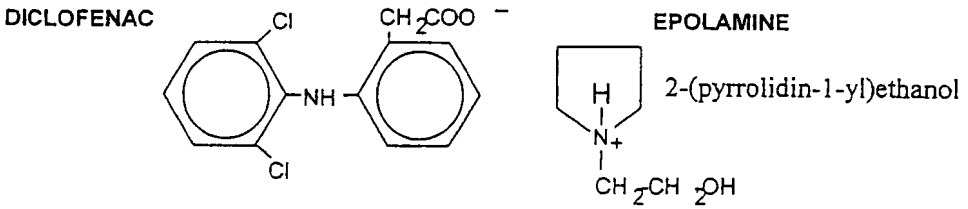
Molecular Formula:

$C_{20}H_{24}Cl_2N_2O_3$

Molecular Weight:

411.3

Structural Formula:



Diclofenac, as described above, is the active ingredient in the approved product FLECTOR®PATCH (diclofenac epolamine topical patch) 1.3% as can be seen from Exhibit 1, being a copy of the approved labeling for the approved product.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

FLECTOR®PATCH (diclofenac epolamine topical patch) 1.3% was subject to regulatory review under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

FLECTOR®PATCH (diclofenac epolamine topical patch) 1.3% received permission for commercial marketing or use under Section 505(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355(b) upon approval of NDA 21-344 on January 31, 2007.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient in the product FLECTOR®PATCH is diclofenac epolamine which has not been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act prior to approval of NDA 21-344 on January 31, 2007.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to §1.720(f) and an identification of the date of the last day on which the application could be submitted.

The product was approved on January 31, 2007, and the last day within the sixty day period permitted for submission of an application for patent term extension is April 1, 2007.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

The complete identification of the patent for which an extension is being sought is as follows:

Inventors:	Antonio Ziggiotti Michele Di Schiena
U.S. Patent No.:	4,948,805
Issue Date:	August 14, 1990
Expiration Date:	November 9, 2007

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A full copy of U.S. Patent No. 4,948,805, for which extension is being sought, is attached as Exhibit 2.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

No disclaimer or reexamination certificate has issued for U.S. Patent No. 4,948,805.

A Certificate of Correction to change the Assignee was issued on January 7, 1992 and is attached as Exhibit 3.

A copy of the maintenance fee statement showing timely payments of each maintenance fee when due is attached as Exhibit 4.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

(i) The approved product, if the listed claims include any claim to the approved product.

(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and

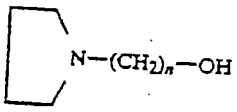
(iii)The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product;

Claims of U.S. Patent No. 4,948,805 read on (i) the chemical composition of the approved product and (ii) pharmaceutical compositions comprising the approved product. Specifically, claim 1 of U.S. Patent No. 4,948,805 as issued reads directly on the active component of the approved product, and is sufficient to support this request for extension of patent term. Additionally, the pharmaceutical composition of claims 2 and 3 as issued read on the approved product.

Claims to the Approved Product

As issued product claim 1 of U.S. Patent No. 4,948,805 reads **as follows**:

1. A water soluble salt, comprising:
diclofenac 2.[(.2,6-dichlorophenyl)-amino-]benzeneacetic acid); and
a cyclic organic base having the formula



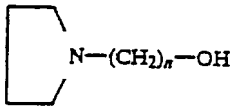
wherein n is 2.

The chemical name for the active ingredient of FLECTOR®PATCH is diclofenac 2[(2,6-dichlorophenyl)-amino-]benzeneacetic acid, 2(-pyrrolidin-1-yl)ethanol salt as can be seen at page 2 of this Request and on the approved label of Exhibit 1. This is identical to the chemical

name for diclofenac epolamine as recited in claim 1. Thus, claim 1 as **issued** clearly "reads on" the approved product.

As issued product claim 2 reads as follows:

2. A pharmaceutical composition comprising a therapeutically active quantity of a water soluble salt of diclofenac and a cyclic organic base having the formula



wherein n is 2, together with a pharmaceutically acceptable excipient.

Issued composition claim 2 would be understood by one of ordinary skill in the art to clearly and unambiguously read on the approved product.

As set forth on the first page of Exhibit 1, the approved product contains as inactive ingredients: 1,3-butylene glycol, dihydroxyaluminum aminoacetate, disodium edentate, D-sorbitol, fragrance (Dalin PH), gelatin, kaolin, methylparaben, polysorbate 80, povidone, propylene glycol, propylparaben, sodium carboxymethylcellulose, sodium polyacrylate, tartaric acid, titanium dioxide, and purified water.

As issued product claim 3 reads as follows:

3. The composition of claim 2, wherein a quantity of the salt diclofenac and said cyclic organic base corresponding to 10-200 mg of diclofenac per unit dosage is present.

Claim 3, which depends from independent claim 2, clearly reads on the approved product, since in the approved product the quantity of the diclofenac epolamine salt corresponds to 180 mg. of diclofenac per unit dosage.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) **For a patent claiming a human drug, antibiotic, or human biological product;**

(A) The effective date of the investigational new drug (IND) application and the IND number;

The IND application for FLECTOR®PATCH(diclofenac epolamine topical patch) 1.3% was submitted on December 8, 1995 and the IND became effective on December 21, 1995. By letter dated December 29, 1995, the FDA acknowledged receipt of the IND application on December 21, 1995, and assigned IND number 49,459. A copy of this letter is attached as Exhibit 5. This establishes the beginning of the "regulatory review period" under 35 U.S.C. §156 (g)(1) as January 20, 1996.

(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number, and

The NDA for FLECTOR®PATCH(diclofenac epolamine topical patch) 1.3% was initially submitted to the FDA on December 19, 2000 and given NDA number 21-234. The NDA submission was received by the FDA on December 19, 2000, as confirmed by Exhibit 6, which establishes December 18, 2000 as the initial submission date of the NDA for the approved product for purposes of 35 U.S.C. §156(g)(1).

(C) **The date on which the NDA was approved or the Product License issued.**

The NDA was approved by the FDA approval letter sent January 31, 2007 setting the effective date of the approval as the January 31, 2007 date of the letter. A copy of this FDA approval letter is attached as Exhibit 7. This establishes the end of the "regulatory review period" under 35 U.S.C. §1.56(g)(1) as January 31, 2007.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

The regulatory activities undertaken to obtain approval of FLECTOR®PATCH(diclofenac epolamine topical patch) 1.3% commenced with the submission of an Investigational New Drug Application (IND 49,459) on December 8, 1995 to study the use of diclofenac epolamine topical patch in the topical treatment of acute pain due to minor strains, sprains, and contusions. IND 49,459 was received by FDA on December 21, 1995, establishing January 20, 1996, as the effective date on which studies could begin.

The testing phase of the regulatory review period consisted of activities occurring under IND 49,459. These activities included meetings with the FDA and timely submission of documents required by regulation including Annual Reports, Information Amendments, IND Safety Reports (initial and follow-up) and Protocol Amendments.

With the filing of NDA 21-234, the testing phase ended and the approval phase of the regulatory review period began. NDA 21-234 was received by the FDA on December 18, 2000. Many significant regulatory activities occurred during the approval phase, including meetings with the FDA, timely responses to FDA requests for information, submissions of 4-Month Safety Update, and revised draft labeling.

The regulatory review period for FLECTOR®PATCH(diclofenac epolamine topical patch) 1.3% ended with permission for commercial marketing being granted by the FDA on January 31, 2007. All regulatory activities were carried out in a prompt, timely manner in accordance with all applicable statutes and regulations.

Evidence of the numerous and continuous activities which occurred under IND 49,459 and NDA 21-234 is provided as Exhibit 8 which comprises a tabulation setting forth key events

occurring during the testing phase and the approval phase. It is readily apparent from Exhibit 8 that the activities were numerous and ongoing, continuously reflecting the diligent pursuit of FDA approval of NDA 21-234 for FLECTOR®PATCH(diclofenac epolamine topical patch) 1.3%.

The marketing applicant during the applicable regulatory review period has been the IBSA Institut Biochemique S.A. Documents confirming these relationships are believed to be on file with the FDA in connection with the regulatory review proceeding, but convenience copies can be provided if needed upon request.

(12) **A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.**

Statement That The Patent Is Eligible for Extension

Applicant is of the opinion that U.S. Patent 4,948,805 is eligible for extension under 35 U.S.C. 156(a), because it satisfies all of the requirements for such extension as follows:

(1) 35 U.S.C. 156(a)

U.S. Patent 4,948,805 claims the approved product.

(2) 35 U.S.C. 156(a)(1)

Since U.S. Patent No. 4,948,805 was in force on June 8, 1995, it is entitled to a term which is the greater of 20 years from the date on which the earliest application from which priority was filed in the United States, or 17 years from grant 35 U.S.C. 154(c). This patent granted on an earliest filed U.S. application filed on November 9, 1987 and the patent granted on August 14, 1990. The term of 20 years from first U.S. filing is the greater term, and the patent thus expires on November 9, 2007. This application, therefore, has been submitted before the expiration of the patent term.

(3) 35 U.S.C. 156(a)(2)

The term of this patent has never been extended.

(4) 35 U.S.C. 156(a)(3)

This application is submitted by the owner of record in accordance with the requirements of 35 U.S.C. 156(d) and the rules of the U.S. Patent and Trademark Office. Altergon S.A. is the owner of record of the patent through an assignment from Altergon S.A. and Ricefarma SrL recorded February 10, 1988 at Reel 004825, Frame 0014, and an

assignment from Antonio Ziggiotti and Michelle D. Schiena to Altergon S.A. and Ricefarma SrL recorded November 9, 1987 at Reel 004795, Frame 0836.

(5) 35 U.S.C. 156(a)(4)

As evidenced by the January 31, 2007 approval letter from the FDA (Exhibit 7), FLECTOR®PATCH(diclofenac epolamine topical patch) 1.3% was subject to a regulatory review period under Section 505(b) of the Federal Food, Drug and Cosmetic Act before its commercial marketing or use.

(6) 35 U.S.C. 156(a)(5)(A)

The permission for commercial marketing of FLECTOR®PATCH(diclofenac epolamine topical patch) 1.3% after this regulatory review period is the first permitted commercial marketing of FLECTOR®PATCH(diclofenac epolamine topical patch) 1.3% under provision of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) under which the regulatory review period occurred, as confirmed by the absence of any approved NDA for the approved product prior to January 31, 2007.

(7) 35 U.S.C. 156(g)(4)

No other patent has been extended for the same regulatory review period for the product FLECTOR®PATCH(diclofenac epolamine topical patch) 1.3%.

Statement as to Length of Extension Claimed

The term of U.S. Patent No. 4,948,805 should be extended by 1825 days, from November 9, 2007 to November 9, 2012. This extension is calculated on the following basis:

Title 35 U.S.C. 156(c) provides that the term of a patent eligible for extension under subsection (a) shall be extended by the time equal to the regulatory review period

for the approved product which period occurs after the date the patent is issued, except that – (1) each period of the regulatory review period shall be reduced by any period during which the applicant for the patent extension did not act with due diligence; (2) after any such reduction required by paragraph (1), the period of extension shall include only one-half of the time remaining in the period under section 156(g)(1)(B)(i)(the testing period under an IND for a new drug); and (3) the total of the period of extension plus the period remaining in the term of the patent after the date of approval shall not exceed fourteen years. The "regulatory review period" is defined in section 156(g)(1), for a new drug product, as being the sum of (i) the testing period beginning on the date exemption under subsection (i) of section 505 (effective date of the IND) and ending on the date the NDA was initially submitted, and (ii) the approval period beginning on the date the NDA was submitted and ending on the date the NDA was approved. Section 156(g)(6) further provides that if the patent involved was issued after the date of the enactment of this section (September 24, 1984), then the period of extension may not exceed five years.

In context of the implementing regulations of 37 C.F.R. 1.175 with respect to patent term extensions for a human drug product, the patent term extension for FLECTOR®PATCH(diclofenac epolamine topical patch) 1.3% was determined as follows:

Sec. 1.775 Calculation of patent term extension for a human drug, antibiotic drug or human biological product.

If a determination is made pursuant to Sec. 1.750 that a patent for a human drug, antibiotic drug or human biological product is eligible for extension, the term shall be extended by the time as calculated in days in the manner indicated by this section. The patent term extension will run from the original expiration date of the patent or any earlier date set by terminal disclaimer (Sec. 1.321).

U.S. Patent No. 4,948,805 was issued on August 14, 1990 from an earliest filed U.S. application filed on November 9, 1987. Pursuant to 35 U.S.C. 154 (c), this patent is entitled to an original term of 20 years from November 9, 1987, which provides an original expiration date of November 9, 2007.

(b) The term of the patent for a human drug, antibiotic drug or human biological product will be extended by the length of the regulatory review period for the product as determined by the Secretary of Health and Human Services, reduced as appropriate pursuant to paragraphs (d)(1) through (d)(6) of this section.

(c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 U.S.C. 156(g)(1)(B), it is the sum of –

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under section 351 of the Public Health Service Act; and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.

The number of days in the IND testing period of paragraph (c)(1) extends from the effective date of IND 49,459 on January 20, 1996 to the filing of NDA number 21-234 on December 19, 2000 being 1430 days.

The number of days in the NDA approval period of paragraph (c)(2) extends from the filing of NDA number 21-234 on December 19, 2000 to the date of approval of NDA 21-234 on January 31, 2007 being 2233 days.

The regulatory review period is the sum of the periods of paragraphs (c)(1) and (c)(2), being 3663 days.

(d) The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by –

(1) **Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:**

(i) **The number of days in the periods of paragraph (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;**

(ii) **The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;**

(iii) **One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section; half days will be ignored for purposes of subtraction;**

With respect to paragraph (d)(1)(i), **no days** of the periods of paragraphs (c)(1) and (c)(2) were before the August 14, 1990 date on which U.S. Patent No. 4,948,805 issued.

With respect to paragraph (d)(1)(ii), there were **no days** during which applicant did not act with due diligence during the periods of paragraphs (c)(1) and (c)(2), as detailed in section (11) above, as evidenced by the continuous activity during the regulatory review period itemized in Exhibit 8.

With respect to paragraph (d)(1)(iii), one-half of the number of days remaining in the period defined by paragraph (c)(1) after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) is one-half of 1430 days, being 715 days which, ignoring half days, is 715 days.

Subtracting from the regulatory review period of 3663 days as determined above pursuant to section 1.175(c) the number of days determined above with respect to paragraphs (d)(1) (i), (ii) and (iii), the term of the patent extension is 3663 days minus 0 days minus 0 days minus 715 days for a sum total of 2948 days.

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

The original term of U.S. Patent No. 4,948,805 is November 9, 2007 and is not shortened by terminal disclaimer. Adding the 2948 days determined in paragraph (d)(1) to the original term of the patent results in an extended term to December 7, 2015.

(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act;

Adding 14 years to the January 31, 2007 date of the approval of the NDA results in a date of January 31, 2021.

(4) **By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;**

The earlier of December 7, 2015 and January 31, 2021 is December 7, 2015.

(5) If the original patent was issued after September 24, 1984,

(i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer; and

(ii) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date;

The original patent was issued after September 24, 1984. Adding 5 years to the original expiration date of the patent (there was no terminal disclaimer) of November 9, 2007 gives a date of November 9, 2012. The earlier of November 9, 2012 and December 7, 2015 is November 9, 2012.

(6) If the original patent was issued before September 24, 1984, and

(i) If no request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act before September 24, 1984, by-

(A) Adding 5 years to the original expiration date of the patent or earlier date set by terminal disclaimer; and

(B) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(6)(i)(A) of this section with each other and selecting the earlier date; or

(ii) If a request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, or Cosmetic Act before September 24, 1984 and the commercial marketing or use of the product was not approved before September 24, 1984, by –

(A) Adding 2 years to the original expiration date of the patent or earlier date set by terminal disclaimer; and

(B) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(6)(ii)(A) of this section with each other and selecting the earlier date.

Since U.S. Patent No. 4,948,805 issued after September 24, 1984, no further adjustment to the extended term of November 9, 2012 is required.

Thus, as calculated above, the term of U.S. Patent No. 4,948,805 is eligible for a 1825 day extension until November 9, 2012.

(12) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (see §1.765).

Applicant acknowledges a duty to disclose to the Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to any determination of entitlement to the extension sought.

(13) **The prescribed fee for receiving and acting upon the application for extension (see §1.20(j)).**

As noted in the letter of transmittal submitted with this application, the Patent and Trademark Office is authorized to charge the filing fee of $1,120.00 and any additional fees which may be required by this or any other related paper, or credit any overpayment to Deposit Account No. 01-0035.

(14) **The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.**

Please address all inquiries and correspondence relating to this application for patent term extension to:

Jay S. Cinamon
Abelman, Frayne & Schwab
666 Third Avenue, 10th Fl.
New York, New York 10017
(212) 885-9232
(212) 949-9022

Respectfully Submitted,
ABELMAN, FRAYNE & SCHWAB

By: 

Jay S. Cinamon
Registration No. 24,156
Tel. No. (212) 949-9022
Fax No. (212) 949-9190

Date: March 21 ,2007
ABELMAN, FRAYNE & SCHWAB
666 THIRD AVENUE, 10th FLOOR
NEW YORK, NEW YORK 10017
(212) 949-9022
(212) 949-9190

Notar/2 7 07 altergon pat term ext.

03-23-07

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Attorney Docket No.: 599 1338
U.S. Patent No. 4,948,805

THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No.:	~~4,948,945~~	)
Granted:	August 14, 1990	)
Patentees:	Antonio ZIGGIOTTI and Michele DISCHIENA)	)
Assignee:	Altergon, S.A.	)
FOR:	SALT OF DICLOFENAC WITH A PYRROLIDINE COMPOUND AND PHARMACEUTICAL COMPOSITIONS WHICH CONTAIN IT	

Attention: BOX PATENT EXTENSION
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

FEE COVER SHEET FOR
REQUEST FOR EXTENSION OF PATENT TERM
PURSUANT TO 35 U.S.C. §156

Sir:

1. Transmitted herewith is a REQUEST FOR EXTENSION OF PATENT TERM PURSUANT to 35 U.S.C. §156 including Exhibits 1-8 (3 sets).

2. Constructive Petition

☒ EXCEPT for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 01-0035. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. §1.136(a)(3).

STATEMENT OF FILING BY EXPRESS MAIL 37 C.F.R. §1.10

This correspondence is being deposited with the United States Postal Service on March 21, 2007 in an envelope as "Express Mail Post Office to Addressee" Mailing Label No.: ER 059 678 238 US addressed to the Honorable Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

03/26/2007 AADOF01 00000008 07117823
01 FC:1457 1120.00 OP

3. Fee Calculation (37 C.F.R. §1.16)

Fee for Patent Term Extension	$1,120.00
Reduction by ½ for Small Entity	$ _____
TOTAL FEE =	$ 1,120.00

4. Fee Payment

☒ Enclosed herewith is a check in the amount of $1,120.00 to cover the fee for filing the Request for Patent Term Extension Under 37 C.F.R. §1.20(j).

☒ The Commissioner is hereby authorized to charge any additional fees which may be required, including fees due under 37 C.F.R. §§1.16 and 1.17, or credit any overpayment to Deposit Account No. 01-0035.

Respectfully Submitted,

ABELMAN, FRAYNE & SCHWAB

Date: March 21, 2007

By: Jay S. Cinamon

JAY S. CINAMON
Registration No. 24,156
Tel. No. (212) 949-9022
Fax No. (212) 949-9190

ABELMAN, FRAYNE & SCHWAB
CUSTOMER NO. 38,137
666 THIRD AVENUE, 10th Fl.
NEW YORK, NEW YORK 10017

JSC:bk

PATENT DOCKET 599 1338

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENTEES: ANTONIO ZIGGIOTTI ET AL.
Examiner: John M. Ford

Patent No.: 4,948,805
Granted: August 14, 1990
Group Art Unit:
Docket No.: 599 1338
Old Docket No.:

For: SALT OF DICLOFENAC WITH A PYRROLIDINE COMPOUND AND PHARMACEUTICAL COMPOSITIONS WHICH CONTAIN IT

Hon. Commissioner of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

POWER OF ATTORNEY BY ASSIGNEE OF ENTIRE INTEREST (REVOCATION OF PRIOR POWERS)

As Assignee of Entire Interest for the above identified

[ ] application,
[X] patent,

REVOCATION OF PRIOR POWERS OF ATTORNEY

I hereby revoke all powers of attorney previously given; and

NEW POWER OF ATTORNEY

I hereby appoint the following attorney(s) and/or agent(s) to prosecute and transact all business in the Patent and Trademark Office connected therewith.

Jeffrey A. Schwab, Reg. No. 24,490
Thomas E. Spath, Reg. No. 25,928
Joseph J. Catanzaro, Reg. No. 25,837
Alan D. Gilliland, Reg. No. 26,549
David Toren, Reg. No. 19,468
Jay S. Cinamon, Reg. No. 24,156
Jerry D. Dainow, Reg. No. 22,959
Anthony J. Natoli, Reg. No. 36,223
Anthony A. Coppola, Reg. No. 41,493
Alexander Zinchuk, Reg. No. 30,541

(Check the following item, if applicable)

SEND CORRESPONDENCE TO:
Jay S. Cinamon
ABELMAN, FRAYNE & SCHWAB
666 Third Avenue, 10th Fl.

New York, New York 10017-5612

DIRECT TELEPHONE CALLS TO:
Jeffrey A. Schwab, Thomas E. Spath, Joseph J. Catanzaro, Jay S. Cinamon, Jerry D. Dainow
Alan D. Gilliland, David Toren, Alexander Zinchuk
Anthony A. Coppola or Anthony J. Natoli at (212) 949-9022

Name of Assignee of Entire Interest:

Altergon, S.A.
LUGANO SWITZERLAND

Address:

Recorded in PTO on: February 10,1988
Reel: 004825
Frame 0014

[ ] Recorded herewith

ASSIGNEE CERTIFICATION

Attached to this power is a "CERTIFICATE UNDER 37 CFR 3.73(B)."

(Signature)

Date: March 12, 2007

AVV. GIAMPIERO BERRA
(type or print name of person authorized to sign on behalf of assignee)

ALTERGON, S.A.
Avv. Giampiero Berra, Sole Director

NOTE: The assignee of the entire interest may revoke previous powers and be represented by an attorney of his or her selection. 37 CFR 1.36.

STATEMENT UNDER 37 CFR 3.73(b)

PATENTEE ZIGGIOTTI ET AL.:
Patent No.: 4,948,805 Grant Date: August 14, 1990
Entitled: SALT OF DICLOFENAC WITH A PYRROLIDINE COMPOUND AND PHARMACEUTICAL COMPOSITIONS WHICH CONTAIN IT

ALTERGON, S.A., a _____ corporation with a place of business at LUGANO SWITZERLAND
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. X the assignee of the entire right, title, and interest; or

2. _an assignee of less than the entire right, title and interest.
The extent (by percentage) of its ownership interest is _____%

in the patent application/patent identified above by virtue of either:

A. [X]An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 004825, Frame 0014, or for which a copy thereof is attached.

OR

B. [ ]A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
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[ ] Additional documents in the chain of title are listed on a supplemental sheet.

[ ]Copies of assignments or other documents in the chain of title are attached.

The undersigned, whose title is below, is authorized to sign on behalf of the corporate assignee.

[NOTE:A separate copy (i.e., the original assignment document or a true copy of the original document) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.08

_____

(Signature) _____

AVV. GIAMPIERO BERRA
(typed or printed name)

_____

ALTERGON S.A.,
Avv. Giampiero Berra, Sole Director

Exhibit 1

Cardiovascular Risk

• NSAIDs[1] may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See **WARNINGS** and **CLINICAL TRIALS**).

• Flector® Patch is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

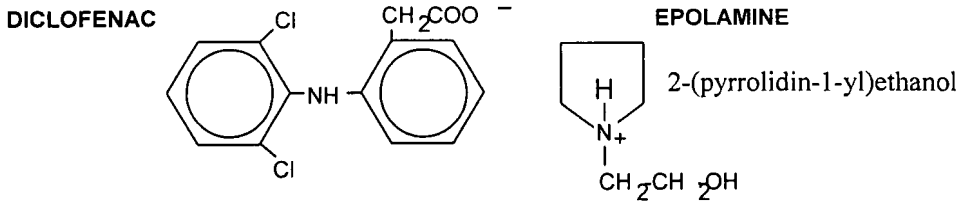
Gastrointestinal Risk

• NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (See **WARNINGS**).

DESCRIPTION

Flector® Patch (10 cm x 14 cm) is comprised of an adhesive material containing 1.3% diclofenac epolamine which is applied to a non-woven polyester felt backing and covered with a polypropylene film release liner. The release liner is removed prior to topical application to the skin.

Diclofenac epolamine is a non-opioid analgesic chemically designated as 2-[(2,6-dichlorophenyl) amino]benzeneacetic acid, (2-(pyrrolidin-1-yl) ethanol salt, with a molecular formula of $C_{20}H_{24}Cl_2N_2O_3$ (molecular weight 411.3), an n-octanol/water partition coefficient of 8 at pH 8.5, and the following structure:



Each adhesive patch contains 180 mg of diclofenac epolamine (13 mg per gram adhesive) in an aqueous base. It also contains the following inactive ingredients: 1,3-butylene glycol, dihydroxyaluminum aminoacetate, disodium edetate, D-sorbitol, fragrance (Dalin PH), gelatin, kaolin, methylparaben, polysorbate 80, povidone, propylene glycol, propylparaben, sodium carboxymethylcellulose, sodium polyacrylate, tartaric acid, titanium dioxide, and purified water.

[1] Throughout this package insert, the term NSAID refers to a non-aspirin non-steroidal anti-inflammatory drug.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Flector® Patch applied to intact skin provides local analgesia by releasing diclofenac epolamine from the patch into the skin. Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID). In pharmacologic studies, diclofenac has shown anti-inflammatory, analgesic, and antipyretic activity. As with other NSAIDs, its mode of action is not known; its ability to inhibit prostaglandin synthesis, however, may be involved in its anti-inflammatory activity, as well as contribute to its efficacy in relieving pain associated with inflammation.

Pharmacokinetics

Absorption

Following a single application of Flector Patch on the upper inner arm, peak plasma concentrations of diclofenac (range 0.7 – 6 ng/mL) were noted between 10 – 20 hours of application. Plasma concentrations of diclofenac in the range of 1.3 – 8.8 ng/mL were noted after five days with twice-a-day Flector Patch application.

Distribution

Diclofenac has a very high affinity (>99%) for human serum albumin.

Metabolism and Excretion

The plasma elimination half-life of diclofenac after application of Flector Patch is approximately 12 hours. Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites.

CLINICAL STUDIES

Efficacy of Flector® Patch was demonstrated in two of four studies of patients with minor sprains, strains, and contusions. Patients were randomly assigned to treatment with Flector® Patch, or a placebo patch identical to Flector® Patch minus the active ingredient. In the first of these two studies, patients with ankle sprains were treated once daily for a week. In the second study, patients with sprains, strains and contusions were treated twice daily for up to two weeks. Pain was assessed over the period of treatment. Patients treated with Flector® Patch experienced a greater reduction in pain as compared to patients randomized to placebo patch as evidenced by the responder curves presented below.

Figure 1: Patients Achieving Various Levels of Pain Relief at Day 3; 14-Day Study

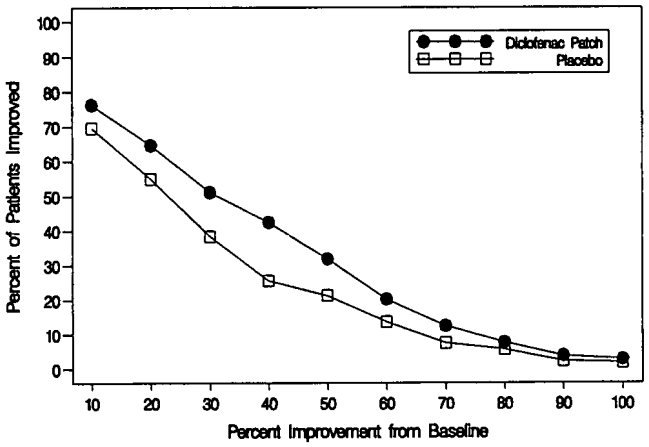


Figure 2: Patients Achieving Various Levels of Pain Relief at End of Study; 14-Day Study

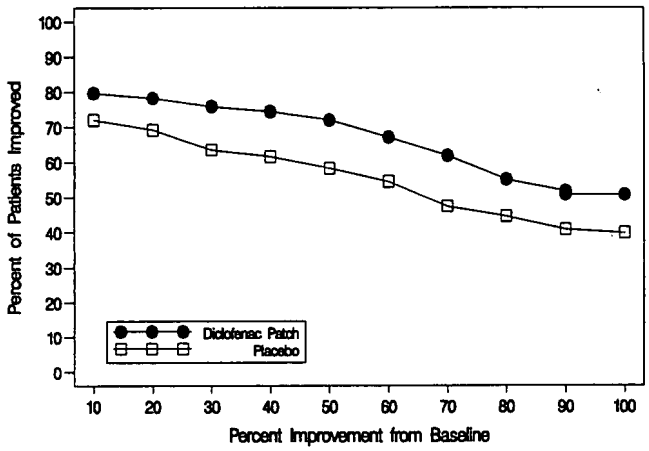


Figure 3: Patients Achieving Various Levels of Pain Relief at Day 3; 7-Day Study

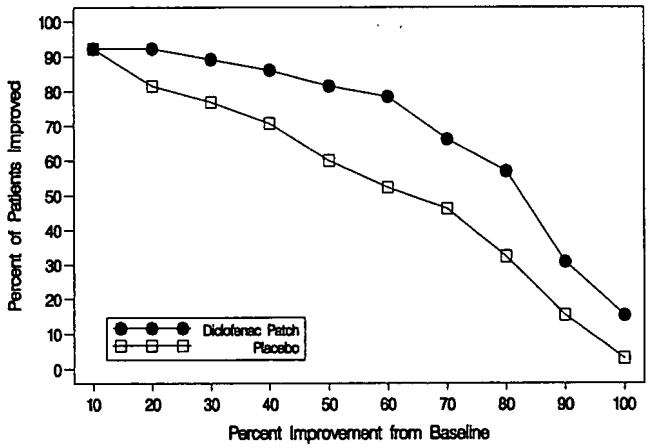
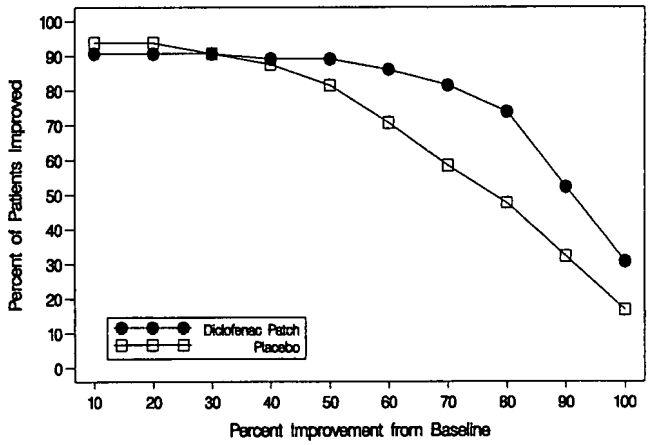


Figure 4: Patients Achieving Various Levels of Pain Relief at End of Study; 7-Day Study



INDICATION AND USAGE

Carefully consider the potential benefits and risks of Flector® Patch and other treatment options before deciding to use Flector® Patch. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

Flector® Patch is indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions.

CONTRAINDICATIONS

Flector® Patch is contraindicated in patients with known hypersensitivity to diclofenac.

Flector® Patch should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see **WARNINGS - Anaphylactoid Reactions**, and **PRECAUTIONS - Preexisting Asthma**).

Flector® Patch is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

Flector® Patch should not be applied to non-intact or damaged skin resulting from any etiology e.g. exudative dermatitis, eczema, infected lesion, burns or wounds.

WARNINGS

CARDIOVASCULAR EFFECTS

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see **GI WARNINGS**).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see **CONTRAINDICATIONS**).

Hypertension

NSAIDs, including Flector® Patch, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including Flector® Patch, should be used with caution in patients with

hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema
Fluid retention and edema have been observed in some patients taking NSAIDs. Flector® Patch should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Effects- Risk of Ulceration, Bleeding, and Perforation
NSAIDs, including Flector® Patch, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease
No information is available from controlled clinical studies regarding the use of Flector® Patch in patients with advanced renal disease. Therefore, treatment with Flector® Patch is not recommended in these patients with advanced renal disease. If Flector® Patch therapy is initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid Reactions
As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to Flector® Patch. Flector® Patch should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see **CONTRAINDICATIONS** and **PRECAUTIONS - Preexisting Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions
NSAIDs, including Flector® Patch, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy
In late pregnancy, as with other NSAIDs, Flector® Patch should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General
Flector® Patch cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of Flector® Patch in reducing inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effects
Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including Flector® Patch. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with Flector® Patch. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), Flector® Patch should be discontinued.

Hematological Effects
Anemia is sometimes seen in patients receiving NSAIDs. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including Flector® Patch, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving Flector® Patch who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting Asthma
Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, Flector® Patch should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Eye Exposure
Contact of Flector® Patch with eyes and mucosa, although not studied, should be avoided. If eye contact occurs, immediately wash out the eye with water or saline. Consult a physician if irritation persists for more than an hour.

Accidental Exposure in Children
Even a used Flector® Patch contains a large amount of diclofenac epolamine (as much as 170 mg). The potential therefore exists for a small child or pet to suffer serious adverse effects from chewing or ingesting a new or used Flector® Patch. It is important for patients to store and dispose of Flector® Patch out of the reach of children and pets.

Information for Patients
Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

1. Flector® Patch, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Cardiovascular Effects**).

2. Flector® Patch, like other NSAIDs, may cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Gastrointestinal Effects: Risk of Ulceration, Bleeding, and Perforation**).

3. Flector® Patch, like other NSAIDs, may cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be

alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.

4. Patients should be instructed to promptly report signs or symptoms of unexplained weight gain or edema to their physicians (see **WARNINGS, Cardiovascular Effects**).

5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

6. Patients should be informed of the signs of an anaphylactoid reaction (e.g. difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see **WARNINGS).**

7. In late pregnancy, as with other NSAIDs, Flector® Patch should be avoided because it may cause premature closure of the ductus arteriosus.

8. Patients should be advised not to use Flector® Patch if they have a aspirin-sensitive asthma. Flector® Patch, like other NSAIDs, could cause severe and even fatal bronchospasm in these patients (see **PRECAUTIONS, Preexisting asthma**). Patients should discontinue use of Flector® Patch and should immediately seek emergency help if they experience wheezing or shortness of breath.

9. Patients should be informed that Flector® Patch should be used only on intact skin.

10. Patients should be advised to avoid contact of Flector® Patch with eyes and mucosa. Patients should be instructed that if eye contact occurs, they should immediately wash out the eye with water or saline, and consult a physician if irritation persists for more than an hour.

11. Patients and caregivers should be instructed to wash their hands after applying, handling or removing the patch.

12. Patients should be informed that, if Flector® Patch begins to peel off, the edges of the patch may be taped down.

13. Patients should be instructed not to wear Flector® Patch during bathing or showering. Bathing should take place in between scheduled patch removal and application (see **DOSAGE AND ADMINISTRATION**).

14. Patients should be advised to store Flector® Patch and to discard used patches out of the reach of children and pets. If a child or pet accidentally ingests Flector® Patch, medical help should be sought immediately (see **PRECAUTIONS, Accidental Exposure in Children**).

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs, should have their CBC and a chemistry profile checked periodically. If clinical

signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, Flector® Patch should be discontinued.

Drug Interactions

ACE-inhibitors

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Aspirin

When Flector® Patch is administered with aspirin, the binding of diclofenac to protein is reduced, although the clearance of free diclofenac is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of diclofenac and aspirin is not generally recommended because of the potential of increased adverse effects.

Diuretics

Clinical studies, as well as post marketing observations, have shown that Flector® Patch may reduce the natriuretic effect-of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see **WARNINGS, Renal Effects**), as well as to assure diuretic efficacy.

Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Warfarin

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of either diclofenac epolamine or Flector Patch.

Mutagenesis

Diclofenac epolamine is not mutagenic in *Salmonella Typhimurium* strains, nor does it induce an increase in metabolic aberrations in cultured human lymphocytes, or the frequency of micronucleated cells in the bone marrow micronucleus test performed in rats.

Impairment of Fertility
Male and female Sprague Dawley rats were administered 1, 3, or 6 mg/kg/day diclofenac epolamine via oral gavage (males treated for 60 days prior to conception and during mating period, females treated for 14 days prior to mating through day 19 of gestation). Diclofenac epolamine treatment with 6 mg/kg/day resulted in increased early resorptions and postimplantation losses; however, no effects on the mating and fertility indices were found. The 6 mg/kg/day dose corresponds to 3-times the maximum recommended daily exposure in humans based on a body surface area comparison.

Pregnancy
Teratogenic Effects. Pregnancy Category C.
Pregnant Sprague Dawley rats were administered 1, 3, or 6 mg/kg diclofenac epolamine via oral gavage daily from gestation days 6-15. Maternal toxicity, embryotoxicity, and increased incidence of skeletal anomalies were noted with 6 mg/kg/day diclofenac epolamine, which corresponds to 3-times the maximum recommended daily exposure in humans based on a body surface area comparison. Pregnant New Zealand White rabbits were administered 1, 3, or 6 mg/kg diclofenac epolamine vial oral gavage daily from gestation days 6-18. No maternal toxicity was noted; however, embryotoxicity was evident at 6 mg/kg/day group which corresponds to 6.5-times the maximum recommended daily exposure in humans based on a body surface area comparison.

There are no adequate and well-controlled studies in pregnant women. Flector Patch should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects
Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Male rats were orally administered diclofenac epolamine (1, 3, 6 mg/kg) for 60 days prior to mating and throughout the mating period, and females were given the same doses 14 days prior to mating and through mating, gestation, and lactation. Embryotoxicity was observed at 6 mg/kg diclofenac epolamine (3-times the maximum recommended daily exposure in humans based on a body surface area comparison), and was manifested as an increase in early resorptions, post-implantation losses, and a decrease in live fetuses. The number of live born and total born were also reduced as was F1 postnatal survival, but the physical and behavioral development of surviving F1 pups in all groups was the same as the deionized water control, nor was reproductive performance adversely affected despite a slight treatment-related reduction in body weight.

Labor and Delivery
In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of Flector® Patch on labor and delivery in pregnant women are unknown.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human-milk and because of the potential for serious adverse reactions in nursing infants from Flector® Patch, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Clinical studies of Flector® Patch did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Diclofenac, as with any NSAID, is known to be substantially excreted by the kidney, and the risk of toxic reactions to Flector® Patch may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken when using Flector® Patch in the elderly, and it may be useful to monitor renal function.

ADVERSE REACTIONS

In controlled trials during the premarketing development of Flector® Patch, approximately 600 patients with minor sprains, strains, and contusions have been treated with Flector® Patch for up to two weeks.

Adverse Events Leading to Discontinuation of Treatment

In the controlled trials, 3% of patients in both the Flector® Patch and placebo patch groups discontinued treatment due to an adverse event. The most common adverse events leading to discontinuation were application site reactions, occurring in 2% of both the Flector® Patch and placebo patch groups. Application site reactions leading to dropout included pruritus, dermatitis, and burning.

Common Adverse Events

Localized Reactions
Overall, the most common adverse events associated with Flector® Patch treatment were skin reactions at the site of treatment.

Table 1 lists all adverse events, regardless of causality, occurring in $\geq$ 1% of patients in controlled trials of Flector® Patch. A majority of patients treated with Flector® Patch had adverse events with a maximum intensity of "mild" or "moderate."

Table 1. Common Adverse Events (by body system and preferred term) in ≥1% of Patients treated with Flector® Patch or Placebo Patch[1]

	Diclofenac N=572		Placebo N=564	
	N	Percent	N	Percent
Application Site Conditions	64	11	70	12
Pruritus	31	5	44	8
Dermatitis	9	2	3	< 1
Burning	2	<1	8	1
Other[2]	22	4	15	3
Gastrointestinal Disorders	49	9	33	6
Nausea	17	3	11	2
Dysgeusia	10	2	3	< 1
Dyspepsia	7	1	8	1
Other[3]	15	3	11	2
Nervous System Disorders	13	2	18	3
Headache	7	1	10	2
Paresthesia	6	1	8	1
Somnolence	4	1	6	1
Other[4]	4	1	3	< 1

[1] The table lists adverse events occurring in placebo-treated patients because the placebo-patch was comprised of the same ingredients as Flector® Patch except for diclofenac. Adverse events in the placebo group may therefore reflect effects of the non-active ingredients.

[2] Includes: application site dryness, irritation, erythema, atrophy, discoloration, hyperhidriosis, and vesicles.

[3] Includes: gastritis, vomiting, diarrhea, constipation, upper abdominal pain, and dry mouth

[4] Includes: hypoaesthesia, dizziness, and hyperkinesia

Foreign labeling describes that dermal allergic reactions may occur with Flector® Patch treatment. Additionally, the treated area may become irritated or develop itching, erythema, edema, vesicles, or abnormal sensation.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Flector® Patch is not a controlled substance.

Physical and Psychological Dependence

Diclofenac, the active ingredient in Flector® Patch, is an NSAID that does not lead to physical or psychological dependence.

OVERDOSAGE

There is limited experience with overdose of Flector® Patch. In clinical studies, the maximum single dose administered was one Flector® Patch containing 180 mg of diclofenac epolamine. There were no serious adverse events.

Should systemic side effects occur due to incorrect use or accidental overdose of this product, the general measures recommended for intoxication with non-steroidal anti-inflammatory drugs should be taken.

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of Flector® Patch and other treatment options before deciding to use Flector® Patch. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

The recommended dose of Flector® Patch is one (1) patch to the most painful area twice a day.

Flector® patch should not be applied to damaged or non-intact skin.

Flector® patch should not be worn when bathing or showering.

HANDLING AND DISPOSAL

Patients and caregivers should wash their hands after applying, handling or removing the patch. Eye contact should be avoided.

HOW SUPPLIED

Flector® Patch is supplied in resealable envelopes, each containing 5 patches (10 cm x 14 cm), with one or two envelopes per box (NDC 64032-xxx-xx). Each individual patch is embossed with "Diclofenac Epolamine Patch 1.3%".

- Each patch contains 180 mg of diclofenac epolamine in an aqueous base (13 mg of active per gram of adhesive or 1.3%).
- The product is intended for topical use only
- Keep out of reach of children and pets.
- The ENVELOPES SHOULD BE SEALED AT ALL TIMES WHEN NOT IN USE.
- Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

Manufacturer: Teikoku Seiyaku Co., Ltd., Sanbonmatsu, Kagawa 769-2695, Japan
Distributor:

Medication Guide
for
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:

- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:

- taking medicines called "corticosteroids" and "anticoagulants"
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:

- different types of arthritis
- menstrual cramps and other types of short-term pain

Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?

Do not take an NSAID medicine:

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

Tell your healthcare provider:

- about all your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**
- if you are breastfeeding. **Talk to your doctor.**

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include:	**Other side effects include:**
• heart attack • stroke • high blood pressure • heart failure from body swelling (fluid retention) • kidney problems including kidney failure • bleeding and ulcers in the stomach and intestine • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • liver problems including liver failure • asthma attacks in people who have asthma	• stomach pain • constipation • diarrhea • gas • heartburn • nausea • vomiting • dizziness

Get emergency help right away if you have any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:

- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.

- Some of these NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

NSAID medicines that need a prescription

Generic Name	Tradename
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol), Flector Patch
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbirofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen* (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naproxyn, Naprelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

* Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAIDS, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

y Pharmaceuticals Inc.
Philadelphia, PA 19101

W10512P001
ET01
Rev 07/05

Ed. V01.07

IBSA

FLECTOR® PATCH
(diclofenac epolamine topical patch)
1.3%

AS 244
154,5x21xZ08

FLECTOR® PATCH
(diclofenac epolamine topical patch)
1.3%

Inactive Ingredients: 1,3-butylene glycol, dihydroxyaluminum aminoacetate, disodium edetate, D-sorbitol, fragrance (Dalin PH), gelatin, kaolin, methylparaben, polysorbate 80, povidone, propylene glycol, propylparaben, sodium carboxymethylcellulose, sodium polyacrylate, tartaric acid, titanium dioxide, and purified water.

DOSAGE: For dosage and full prescribing information, read accompanying product information.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

WARNING: Envelope is not child resistant. Keep used and unused patches out of reach of children and pets.

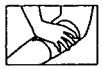
DIRECTIONS FOR USE

Refer to Full Directions Before Using.


Cut the outer seal from the envelope along the dotted line and pull apart the zipper seal.


Remove one FLECTOR® PATCH. **IMPORTANT Reseal after opening** by applying pressure on the zipper seal. The patch adhesive contains water and will dry out if the envelope is left open.


Remove the transparent release liner before application of patch to the skin.


Apply one FLECTOR® PATCH at a time to cover the most painful area.
Change patch once every 12 hours.
Remove patch if irritation occurs. (See full prescribing information.)


Fold used patches so that the adhesive side sticks to itself and safely discard used patches where children and pets cannot get them.

Discard unused patches 3 months after opening envelope.

5 PATCHES (10 CM X 14 CM EACH)

Manufactured for:
IBSA Institut Biochimique SA,
CH-6903 Lugano, Switzerland

Manufactured by:
Teikoku Seiyaku Co., Ltd.
Sanbonmatsu, Kagawa 769-2695
Japan

BAR CODE

FLECTOR® PATCH
(diclofenac epolamine topical patch)
1.3%

Proc. Black C
Process Blue
Reflex Blue
Pantone 485
Blue 294

(USA) xxxx

NDC 64032-XXX-XX

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Rx Only

IBSA

Lot.:

Expiration date:

Ed. 1/01.07

IBSA

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(diclofenac epolamine topical patch)
1.3%

Proc. Black C
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Reflex Blue
Rosin 485
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IBSA

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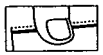
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BAR CODE

(USA) xxxx

AS/277
154.5x27x208

IBSA

FLECTOR® PATCH
(diclofenac epolamine topical patch)
1.3%

NDC 64032-XXX-XX

FLECTOR® PATCH

(diclofenac epolamine topical patch)
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Rx Only

IBSA

Lot.

Expiration date:

IMPORTANT
Reseal after opening

NDC 64032-XXX-XX

FLECTOR® PATCH

(diclofenac epolamine topical patch)
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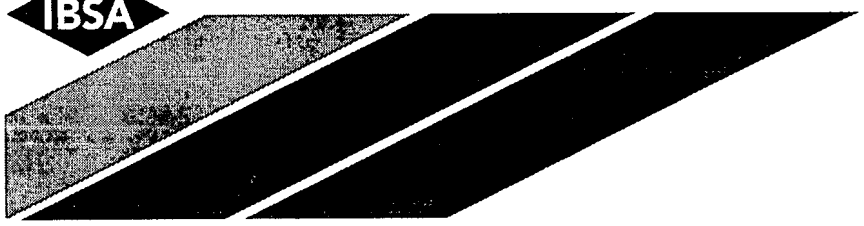
R_x Only

IBSA



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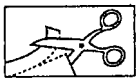

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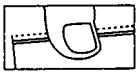

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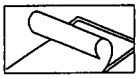

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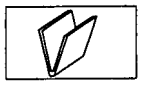

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Japan

BAR CODE

Lot

Exp.

Flector® Patch
(diclofenac epolamine topical patch) 1.3%

RECYCLED

Exhibit 2

United States Patent [19]

Ziggiotti et al.

[11] **Patent Number: 4,948,805**

[45] **Date of Patent: Aug. 14, 1990**

Exhibit 2

[54] **SALT OF DICLOFENAC WITH A PYRROLIDINE COMPOUND AND PHARMACEUTICAL COMPOSITIONS WHICH CONTAIN IT**

[75] Inventors: **Antonio Ziggiotti**, Vezia, Switzerland; **Michele Di Schiena**, Cisliano, Italy

[73] Assignee: **Altergon S. A. & Ricerfarma Srl.**, Italy

[21] Appl. No.: **117,823**

[22] Filed: **Nov. 9, 1987**

[30] **Foreign Application Priority Data**

Nov. 13, 1986 [IT] Italy 22320 A/86

[51] **Int. Cl.**[5] **A61K 31/40**

[52] **U.S. Cl.** **514/428**; 548/574

[58] **Field of Search** 548/570, 574; 546/248; 540/609; 514/428, 315, 212

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,558,690 1/1971 Sallmann 548/485

OTHER PUBLICATIONS

Chemical Abstracts, vol. 102, no. 26, Jul. 1, 1985, p. 336, Abstract no. 225919f.

Primary Examiner—John M. Ford
Assistant Examiner—Zinna Northington-Davis
Attorney, Agent, or Firm—Arnold, White & Durkee

[57] **ABSTRACT**

The salt of diclofenac with a cyclic organic base is prepared by dissolving diclofenac in a suitable organic solvent, adding said cyclic organic base, reacting the two components together, removing the solvent and crystallizing the product obtained.

Said salt is water soluble to an extent from 20% w/v to an extent exceeding 50% w/v, and is used to prepared pharmaceutical compositions preferably in granular form for use by dissolving in water for oral administration.

4 Claims, No Drawings

SALT OF DICLOFENAC WITH A PYRROLIDINE COMPOUND AND PHARMACEUTICAL COMPOSITIONS WHICH CONTAIN IT

DESCRIPTION OF THE TECHNICAL FIELD

This invention relates to the salt of diclofenac with a cyclic organic base and to pharmaceutical compositions which contain it.

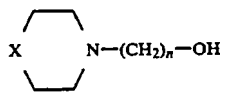
More particularly, the invention relates to the salt of diclofenac with a cyclic organic base in the various pharmaceutical forms, and preferably in granular form for use in extemporaneous solutions for oral administration.

Diclofenac (2[2,6-dichlorophenyl)-amino]benzeneacetic acid) is an anti-inflammatory medicament which has been known for a considerable time and which together with numerous other compounds falls under the general formula of U.S. Pat. No. 3,558,690.

One of the characteristics of these compounds is that they cyclize in an acid environment to give the corresponding indolinones. In order to obtain stabilization of the open form, they are salified with non-toxic organic or inorganic bases as described for example in the aforesaid patent. However, in this patent no information is given regarding the solubility of said salts in water, and notwithstanding the fact that several years have passed since the teachings of the said patent were made available, no aqueous pharmaceutical composition of diclofenac has been marketed.

BRIEF SUMMARY OF THE INVENTION

We have now found that it is possible to obtain a highly water soluble diclofenac salt by salifying diclofenac with a cyclic organic base having the general formula (I)



(I)

in which X is a group of the formula $(CH_2)_m$, in which m is 0 or 1 or 2, or X is oxygen or S or NR, in which R is an alkyl group C_1–C_4, and n is 2 or 3. This is very surprising in the light of the fact that U.S. Pat. No. 3,558,690 comprises salts of diclofenac with bases such as 2-aminoethanol and pyrrolidine which are very close to the bases of the formula (I) from a structural viewpoint, whereas these salts are practically insoluble in water.

In contrast to the tablet form currently used for oral administration one particular unforseable advantage of the salt of diclofenac with a base of formula (I) is that when prepared in granular form and stored in water-impermeable sachets, it enables extemporaneous aqueous solutions to be prepared which while totally maintaining their activity level do not give rise to gastrolesion.

The enormous advantage of such a behaviour which obviates any risk to the patient ingesting the medicament is an obvious considerable merit in terms of its pharmaceutical application.

The salt of diclofenac with a base of formula (1) therefore constitutes a subject of the present invention, a further subject of the invention being pharmaceutical compositions containing a therapeutically useful dosage of said salt.

The process for preparing this salt is extremely simple from an industrial viewpoint, it being characterized by dissolving diclofenac in a suitable organic solvent, adding a base of formula (I), reacting said compounds together at ambient temperature, removing the solvent and crystallising the product obtained.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Suitable organic solvents for dissolving diclofenac are acetone, ethanol and chloroform. The base used in equimolar quantity or in slight excess with respect to the diclofenac. The reaction is conducted at ambient temperature under agitation for a time of between 0.5 and 3 hours. The solvent is removed by distillation under vacuum at a temperature of between 35° and 45° C. The salt is crystallised by treating the distillation residue with hexane or petroleum ether under energetic agitation. The unrefined salt obtained is redissolved in acetone and recrystallised from hexane or petroleum ether.

The solubility characteristics of the salt of diclofenac with hydroxy-ethylpyrrolidine (ID) and with hydroxyethylpiperidine (IP) compared with the salts of diclofenac with sodium (SD), with pyrrolidine (PD) and with 2-aminoethanol (AD) are given in the following table.

Compound	Solubility (% w/v)	Solution pH	Commencement of precipitation
ID	>50	7.5	24 h
IP	>20		
SD	1.36	7.6	
PD	practically insoluble		
AD	practically insoluble		

The salt of diclofenac with a base of formula (I) also has high shelf-life. The pharmaceutical compositions according to the present invention contain a therapeutically active quantity of the salt of diclofenac with a base of formula (I) together with pharmaceutically acceptable liquid or solid excipients of organic or inorganic type, and can be administered orally. Preferably, said compositions contain an active ingredient quantity corresponding to 10–200 mg of diclofenac per unit dosage.

Examples of preferred pharmaceutical forms are granular forms packaged in sachets of water-impermeable material, and are dissolved in a little water to form solutions for oral administration.

In addition to the excipients, said compositions can contain preservatives, stabilizers, wetting agents, emulsifiers, osmotic pressure regulating salts, buffers, dyestuffs, sweeteners and flavorings. They are prepared by known methods and can contain other therapeutic agents.

The following examples are described by way of non-limiting illustration of the present invention.

EXAMPLE 1

Preparation of the salt of diclofenac with hydroxyethylpyrrolidine

14.75 g (49.8 mmoles) of 2-[(2,6-dichlorophenyl)-amino]benzeneacetic acid (diclofenac) were dissolved in acetone (50 ml), and 5.75 g (49.9 mmoles) of freshly

distilled hydroxyethylpyrrolidine were added to the solution obtained.

After keeping the solution under agitation for one hour at ambient temperature, the solvent was removed under vacuum at 40° C.

The oily residue was treated with hexane (100 ml) and the obtained mixture kept under energetic agitation until the oil was transformed into a crystalline solid, which was separated by filtration and dried. 17 g of product were obtained having an M.P. of 57°–58° C. (yield 83% of theoretical).

The unrefined product obtained in this manner was dissolved in acetone (50 ml), decolorized with animal charcoal and filtered. The solution was evaporated under vacuum, and the residue treated with hexane as described heretofore. The salt of diclofenac with hydroxyethylpyrrolidine was obtained in its pure state, with an M.P. of 97.5°–100° C.

EXAMPLE 2

Preparation of the salt of Diclofenac with 1-(2-hydroxyethyl)-piperidine

A solution of 8.9 g of 2--/(2,6-dichloro-phenyl)-amino]-phenylactic acid in 220 ml of ethyl acetate is treated with a solution of 3.88 g of 1-(2-hydroxyethyl)-piperidine in 20 ml ethyl acetate while stirring.

After 30 minutes the clear solution is concentrated under reduced pressure to a volume of 100 ml and diluted with 100 ml diethyl ether. The crystalline 1-(2-hydroxyethyl)-piperidine salt of 2-[(2,6-dichlorophenyl)-amino]-phenylacetic acid precipitates and is filtered off. M.P. 109°–111°; solubility in water: 20% w/v.

EXAMPLE 3

Preparation of a granulate containing the salt of diclofenac with hydroxyethylpyrrolidine

A granulate was prepared having the following composition:

Salt of diclofenac with hydroxyethylmirrolydine	70 mg
Sorbitol	1798 mg
Aspartame	50 mg
Polyethyleneglycol 6000	150 mg
E 124	1 mg
E 110 HC	1 mg
Flavoring	130 mg

70 g of the salt of diclofenac with hydroxyethylpyrrolidine, 1.798 Kg of sorbitol and 50 g of aspartame were mixed together in a steel cube mixer for 20 minutes.

150 g of polyethyleneglycol 6000, 1 g of E 124 and 1 g of E 110 HC were dissolved in 280 ml of boiling water under agitation.

The solid mixture and solution prepared in this manner were mixed together in a fluidized bed granulator using 100 ml of mixing water. The granulate obtained in this manner was sieved through an oscillating screen with a mesh size of 1 mm.

130 g of flavoring was sieved separately with the same screen, and was mixed with the said granulate in a cube mixer for 20 minutes.

The granulate obtained in this manner was dispensed into sachets of water-impermeable material, dispensing 2,2 g of granulate into each sachet.

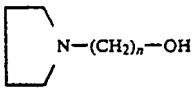
At the moment of use, the contents of each sachet were easily dissolved in a little water to form a drinkable solution which in terms of acid contains 50 mg of diclofenac.

We claim:

1. A water soluble salt, comprising:

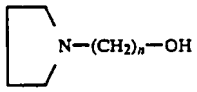
diclofenac (2-[(-2,6-dichlorophenyl)-amino-]benzeneacetic acid); and

a cyclic organic base having the formula



wherein n is 2.

2. A pharmaceutical composition comprising a therapeutically active quantity of a water soluble salt of diclofenac and a cyclic organic base having the formula



wherein n is 2, together with a pharmaceutically acceptable excipient.

3. The composition of claim 2, wherein a quantity of the salt of diclofenac and said cyclic organic base corresponding to 10–200 mg of diclofenac per unit dosage is present.

4. The composition of claim 2, wherein said composition is in granular form and is packaged in a water-impermeable sachet.

* * * * *

Exhibit 3

Exhibit 3

CERTIFICATE OF CORRECTION

PATENT NO. : 4,948,805

DATED : August 14, 1990

INVENTOR(S) : Antonio Ziggiotti and Michele DiSchiena

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the title page:

Change the Assignee [73] from "Altergon S.A. & Ricerfarma Srl., Italy" to --Altergon S.A., Lugano, Switzerland--.

Signed and Sealed this

Seventh Day of January, 1992

Attest:

HARRY F. MANBECK, JR.

Attesting Officer

Commissioner of Patents and Trademarks

Exhibit 4

Exhibit 4

Return To:

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United States Patent and Trademark Office

Patent Bibliographic Data					02/26/2007 05:09 PM
Patent Number:	4948805		**Application Number:**	07117823	
Issue Date:	08/14/1990		**Filing Date:**	11/09/1987	
Title:	SALT OF DICLOFENAC WITH A CYCLIC PYRROLIDINE COMPOUND AND PHARMACEUTIC				
Status:	4th, 8th and 12th year fees paid			**Entity:**	Small
Window Opens:	N/A	**Surcharge Date:**	N/A	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:					
Surcharge Fee Code:					
Most recent events (up to 7):	2002/01/26 2002/01/26 2002/01/23 1998/01/20 1998/01/20 1998/01/16 1994/07/20	Payor Number Assigned. Payer Number De-assigned. Payment of Maintenance Fee, 12th Yr, Small Entity. Payor Number Assigned. Payer Number De-assigned. Payment of Maintenance Fee, 8th Yr, Small Entity. Payment of Maintenance Fee, 4th Yr, Small Entity. --- End of Maintenance History ---			
Address for fee purposes:	N & G PATENT SERVICES VIA BESSO 7 LUGANO, 6900				

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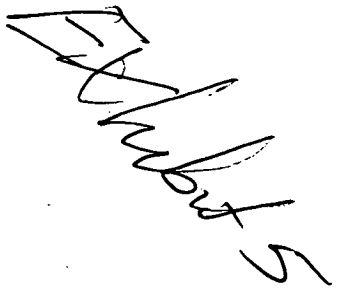

Food and Drug Administration
Rockville MD 20857

Exhibit 5

IND 49,459

Date DEC 29 1995

Institut Biochimique SA (IBSA)
ATTN: Larry J. Caldwell, Ph.D.
165 Gibraltar Court
Sunnyvale, CA 94089

Dear Sir or Madam:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 49,459

Sponsor: Institut Biochimique SA (IBSA)

Name of Drug: Diclofenac Patch, Diclofenac Epolamine 1.3%

Date of Submission: December 8, 1995

Date of Receipt: December 21, 1995

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations). Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon as possible and in no event later than 10 working days after initial receipt of the information and reporting any unexpected fatal or life-threatening experience to the FDA by telephone no later than 3 working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-550)
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this IND, please contact

Sincerely yours,

Patricia C. O'Brien

Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

cc: Original IND - pink
HFD-550 yellow
HFD-550CSO - green

IND ACKNOWLEDGEMENT

Exhibit 6

RECYCLED

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Exhibit 6

Food and Drug Administration
Rockville MD 20857

NDA 21-234

Institut Biochimique SA (IBSA)
Attention: Larry Caldwell, Ph.D.
745-D Camden Avenue
Campbell, CA 95008-4146

Dear Dr. Caldwell:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Diclofenac Epolamine (diclofenac epolamine patch) Patch 1.3%

Review Priority Classification: Standard (S)

Date of Application: December 18. 2000

Date of Receipt: December 19, 2000

Our Reference Number: NDA 21-234

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 16, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 17, 2001 and the secondary user fee goal date will be December 17, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
HFD-550
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
HFD-550
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Barbara Gould, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Leslie Vaccari
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

/s/

Leslie Vaccari
2/14/01 02:12:48 PM

Exhibit 7

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Exhibit 7

NDA 21-234

Institut Biochimique SA
c/o: Clarence E. Jones
8602 Mossford Drive
Huntington Beach, CA 92646

Dear Mr. Jones:

Please refer to your new drug application (NDA) dated December 18, 2000, received December 19, 2000, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Flector® Patch (diclofenac epolamine topical patch) 1.3%

We acknowledge receipt of your submissions dated February 5, 6, and 22, March 16 and 30, April 12 and 18, May 2 and 17, June 6 and 22, August 14, 16, and 23, September 6, October 19, and December 26, 2001, February 8, March 28, and April 4, 2002, July 27, September 5, 12, and 14, October 31, and December 8, 13 and 28, 2006, and January 23, 2007.

The July 27, 2006, submission constituted a complete response to our October 18, 2001, action letter.

This new drug application provides for the use of Flector® Patch (diclofenac epolamine topical patch) 1.3% for the topical treatment of acute pain due to minor strains, sprains, and contusions.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, Medication Guide, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0 through 1 year and deferring pediatric studies for ages 2 through 16 years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing studies shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of acute pain due to minor strains, sprains, and contusions in pediatric patients ages 2 through 16.

   Final Report Submission: January 31, 2011

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitments**."

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence.**"

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Lisa Basham, Regulatory Project Manager, at (301) 301-796-1175.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, MD
Director
Division of Anesthesia, Analgesia, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bob Rappaport
1/31/2007 06:23:19 PM

RECYCLED

Exhibit 8

Critical Events in the Approval Process for DEP Beginning with IND Submission

Activity	Date	Type	Purpose
IND Submission	12.08.1995	Regulatory	Required to initiate clinical trials in U.S.
IND receipt (49,459)	12.29.1995	Regulatory	Required to initiate clinical trials in U.S
Answer from Medical Reviewer (Chin Koerner) about IND content	01.30.1996	Regulatory	Required to initiate clinical trials in U.S
Conference call with FDA	03.21.1996	Regulatory	FDA comments on IND (49,459)
Submission of revised first clinical protocol	09.01.1996	Regulatory	Confirmation of revisions as discussed during the conference call
IND 49,459 Study 01 Start: End: Study Report:	 10.1.1996 08.13.1997 03.15.1998	Clinical	First Phase III clinical investigation for the evaluation of Flector patch efficacy and safety in the treatment of minor sports injuries
FDA Meeting	06.16.1998	Regulatory	End of phase II/phase III meeting: to discuss the results of the first study and agree upon the protocol of the second study
Submission of the protocol of Study 02 to the Agency	August 1998	Clinical	Protocol evaluation
Conference call between the Agency and the Sponsor	11.05.1998	Clinical	Protocol details discussion/confirmation
Request for additional local safety study (photosensitisation)	07.20.1999	Clinical	Photoallergy maximization test on 25 human subjects AMA Lab
IND 49,459 Study 02 Start: End: Study Report:	 03.24.1999 03.23.2000 12.10.2000	Clinical	Second Phase III clinical investigation for the evaluation of Flector patch efficacy and safety in the treatment of minor sports injuries
FDA Meeting (Pre-NDA Meeting)	03.28.2000	Regulatory	Discuss with the FDA the adequacy /completeness of the various sections of the registration doissier and define any additional data to be supplied
Requested additional Study	08.17.2000	Clinical	Evaluation of phototoxicity potential AMA Lab
Requested additional Study	08.17.2000	Clinical	21-day relative comulative irritancy study AMA Lab
Requested additional Study	10.19.2000	Clinical	Influence of exercise on the absorption of Diclofenc Epolamine CRO-PK-00-33
Requested additional Study	Med Sport 2000; 53:275-8	Clinical	Retrospective study in minor sport injuries in children treated with Flector patch
Original NDA submission (21,234)	12.18.2000	Regulatory	
NDA officially accepted at the FDA	12.19.2000	Regulatory	
FDA Requested AMSA (DEP	04.24-27.2001	Inspection	Inspection started 04.26.2001

manufacturere) Inspection			
Teleconferences between FDA and Sponsor	06.29.2001 07.16.2001 07.24.2001	Regulatory	Supply of additional data/information
FDA inspected Teikoku (Product manufacturer)	08.21-24.2001	Inspection	
Additional statistical analysis of efficacy data of studies 01 and 02, as request by FDA	09.06.2001	Clinical	New statistical analysis of daily pain scores (as recoreded by the patients in the two phase III studies)
FDA non approval letter	10.18.2001	Regulatory	
FDA meeting	11.20.2001	Regulatory	Discuss the deficiencies identified by FDA in the non approval letter, expecially from a clinical view point
Requested additional Clinical Study Start: End Study Report:	 February 2002 January 2004 February 2006	Clinical Study Phase III	00GB/Fp05 (UK/D study): new phase II study in minor sports injury
Submission of Amendment 12, in response to the non-approval letter	03.28.2002	Regulatory	Submission of re-analysis of the efficacy data in the light of the deficiencies highlighted by FDA in the non approval letter
Requested additional Study	11.14.2002	Clinica Phase I	Epicutaneous absorption CRO PK 02-76, single vs staedy state diclofenac blood level, for labeling purposes
FDA second non approval letter	04.16.2003	Regulatory	
Submission of amendment 13: New clinical data in minor sports injury (study 00GB/Fp05 and study 05-05-08) and full response to deficiencies of non approval letter of 04.16.2003	07.27.2006	Regulatory	
FDA clinical site inspections	01.08-11.2007 at Dr. Ottstadt 01.15-19.2007 at Dr. Maille	Inspection	GCP inspections
FDA approval letter of 01.31.2007	01.31.2007	Regulatory	
Post approval commitment: Deferred pediatric study (ages of 2 to 16)	Deadline for report submission: January, 31, 2011	Clinical	